Roflumilast Cream, a Once-Daily, Potent Phosphodiesterase-4 Inhibitor, in Chronic Plaque Psoriasis Patients: Efficacy and Safety From DERMIS-1 and DERMIS-2 Phase 3 Trials

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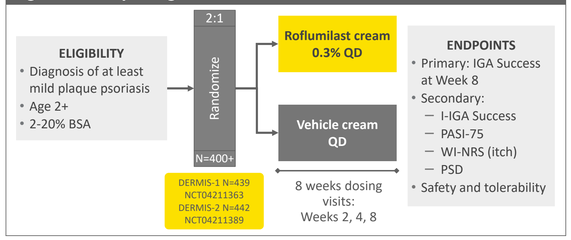
INTRODUCTION

- No novel nonsteroidal topical therapies for plaque psoriasis have been approved in more than 2 decades, and available topical treatments are less than ideal, necessitating a trade-off between efficacy and tolerability[1]
- Roflumilast is a highly potent phosphodiesterase-4 inhibitor being investigated as a once-daily, nonsteroidal, topical treatment for various dermatologic conditions
  - In a phase 2b, randomized, double-blind, vehicle-controlled trial, roflumilast cream provided significant and rapid improvement of psoriasis, including demonstrated efficacy for intertriginous plaques and rapid reduction of itch[2]
- Efficacy and safety results from DERMIS-1 and DERMIS-2, 2 identical phase 3, randomized, double-blind, vehicle-controlled studies of once-daily roflumilast cream 0.3% in patients with psoriasis are presented

METHODS

- Randomized, double-blind, vehicle-controlled, multicenter, phase 3 studies
- DERMIS-1 and DERMIS-2 had identical study design and endpoints (**Figure 1**)

Figure 1. Study Design



BSA: body surface area; IGA: Investigator Global Assessment; I-IGA: intertriginous-Investigator Global Assessment; PASI-75: Psoriasis Area and Severity Index-75% reduction; PSD: Psoriasis Symptom Diary; QD: once daily; WI-NRS: Worst Itch-Numeric Rating Scale.

RESULTS

- Few patients discontinued due to adverse events (**Table 1**)

Table 1. Patient Disposition

	DERMIS-1		DERMIS-2	
Patients, n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (n=152)
Completed	255 (89.2)	133 (86.9)	264 (91.0)	131 (86.2)
Prematurely discontinued	31 (10.8)	20 (13.1)	26 (9.0)	21 (13.8)
Reason for discontinuation				
Withdrawal by patient	11 (3.8)	11 (7.2)	10 (3.4)	11 (7.2)
Physician decision	0	1 (0.7)	0	0
Noncompliance	0	0	0	1 (0.7)
Protocol violation	1 (0.3)	0	0	0
Lost to follow-up	12 (4.2)	4 (2.6)	15 (5.2)	7 (4.6)
Adverse event	5 (1.7)	2 (1.3)	1 (0.3)	2 (1.3)
Pregnancy	1 (0.3)	0	0	0
Other	1 (0.3)	2 (1.3)	0	0

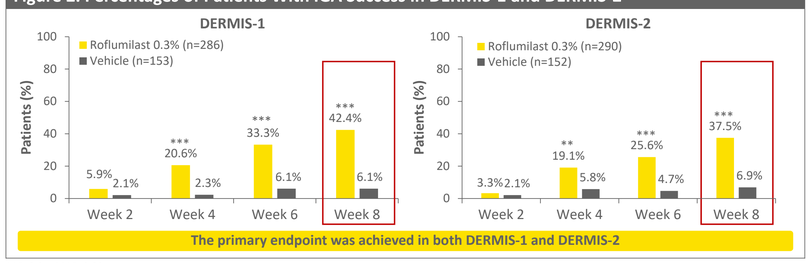
Table 2. Baseline Disease Characteristics (ITT Population)

	DERMIS-1		DERMIS-2	
n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (n=152)
Age, mean (SD), years	47.6 (14.09)	48.7 (15.77)	46.9 (15.07)	47.1 (14.07)
Sex				
Male, n (%)	189 (66.1)	96 (62.7)	176 (60.7)	100 (65.8)
Female, n (%)	97 (33.9)	57 (37.3)	114 (39.3)	52 (34.2)
Race, n (%)				
American Indian or Alaska Native	4 (1.4)	1 (0.7)	0	1 (0.7)
Asian	21 (7.3)	11 (7.2)	20 (6.9)	9 (5.9)
Black or African American	8 (2.8)	8 (5.2)	13 (4.5)	9 (5.9)
Native Hawaiian or Other Pacific Islander	2 (0.7)	0	3 (1.0)	1 (0.7)
White	234 (81.8)	124 (81.0)	240 (82.8)	126 (82.9)
Not reported	4 (1.4)	3 (2.0)	5 (1.7)	2 (1.3)
Other	11 (3.8)	5 (3.3)	8 (2.8)	4 (2.6)
More than 1 race	2 (0.7)	1 (0.7)	1 (0.3)	0
Psoriasis-affected BSA, mean (SD), %	6.3 (4.38)	7.4 (4.76)	7.1 (4.84)	7.7 (5.05)
PASI score, mean (SD)	6.3 (3.15)	6.8 (3.70)	6.5 (3.22)	7.0 (3.52)
WI-NRS score, mean (SD)	5.7 (2.75)	5.7 (2.84)	5.8 (2.61)	6.1 (2.75)
WI-NRS score ≥4, n (%)	218 (76.2)	115 (75.2)	229 (79.0)	116 (76.3)
PSD total score, mean (SD)	72.1 (42.75)	73.4 (41.29)	69.3 (40.66)	77.4 (41.24)
IGA score, n (%)				
2 (mild)	51 (17.8)	20 (13.1)	50 (17.2)	24 (15.8)
3 (moderate)	206 (72.0)	122 (79.7)	220 (75.9)	118 (77.6)
4 (severe)	29 (10.1)	11 (7.2)	20 (6.9)	10 (6.6)
I-IGA score ≥2, n (%)	n=63	n=32	n=53	n=31
2 (mild)	33 (52.4)	16 (50.0)	25 (47.2)	13 (41.9)
3 (moderate)	27 (42.9)	16 (50.0)	27 (50.9)	17 (54.8)
4 (severe)	3 (4.8)	0	1 (1.9)	1 (3.2)

BSA: body surface area; IGA: Investigator Global Assessment; I-IGA: Intertriginous-Investigator Global Assessment; ITT: intent-to-treat; PASI: Psoriasis Area Severity Index; PSD: Psoriasis Symptoms Diary; SD: standard deviation; WI-NRS: Worst Itch-Numeric Rating Scale.

- Robust efficacy on IGA Success in both phase 3 studies (**Figure 2**)

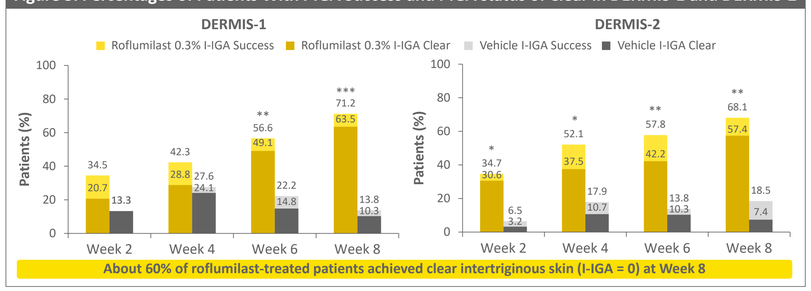
Figure 2. Percentages of Patients With IGA Success in DERMIS-1 and DERMIS-2



**P<0.01; ***P<0.001.
IGA Success = clear or almost clear with at least a 2-grade improvement from baseline. Intent-to-treat population; missing scores imputed using multiple imputations.
IGA: Investigator Global Assessment.

- Roflumilast was highly effective for intertriginous plaques in DERMIS-1 and DERMIS-2 (**Figure 3**)

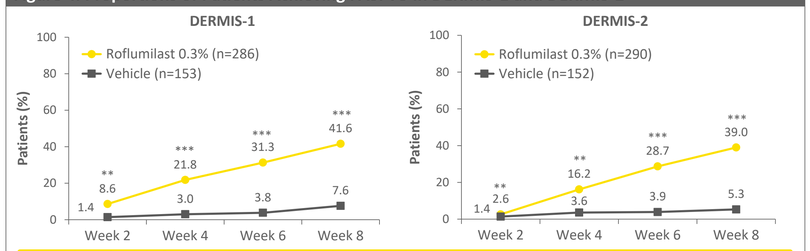
Figure 3. Percentages of Patients With I-IGA Success and I-IGA status of Clear in DERMIS-1 and DERMIS-2



P values for I-IGA success: *P<0.05; **P<0.01; ***P<0.001.
IGA Success = clear or almost clear with at least a 2-grade improvement from baseline. I-IGA intent-to-treat population: patients with intertriginous area involvement with severity of the intertriginous lesions at least mild (I-IGA ≥2) at baseline. Observed data. I-IGA: Intertriginous-Investigator Global Assessment.

- Roflumilast was statistically superior to vehicle for improvement of psoriasis (PASI-75) at all timepoints (**Figure 4**)

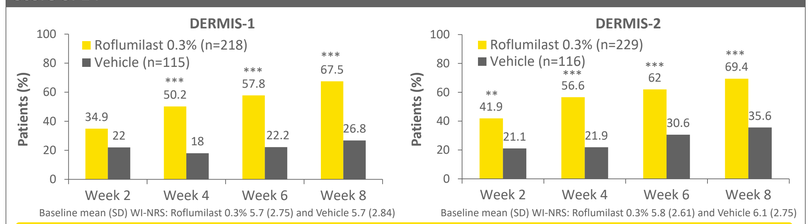
Figure 4. Proportions of Patients Achieving PASI-75 in DERMIS-1 and DERMIS-2



**P<0.01; ***P<0.001.
Intent-to-treat population; missing scores imputed using multiple imputations. PASI-75: Psoriasis Area Severity Index-75% reduction.

- Rapid itch response in both DERMIS-1 and DERMIS-2 (**Figure 5**)

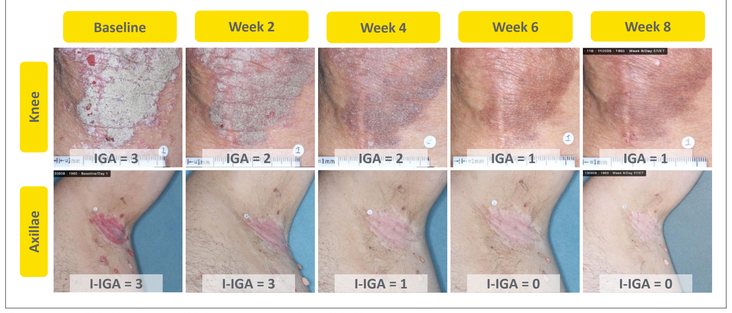
Figure 5. Proportion of Patients Who Achieved a ≥4-Point Improvement in WI-NRS From Baseline Score of ≥4



**P<0.01; ***P<0.001.
Evaluated in a subset of the intent-to-treat population of patients with WI-NRS pruritus score ≥4 at baseline; missing scores imputed using multiple imputations.
SD: standard deviation; WI-NRS: Worst Itch-Numeric Rating Scale.

- Patient examples illustrating efficacy of roflumilast cream 0.3% from DERMIS-1 and DERMIS-2 are shown in **Figure 6**

Figure 6. Representative Photos of Patients Treated With Roflumilast Cream 0.3%



IGA: Investigator Global Assessment; I-IGA: intertriginous-Investigator Global Assessment.

- Roflumilast safety and tolerability were similar to vehicle (**Table 3**)
  - Roflumilast cream demonstrated low rates of application-site adverse events (AEs), treatment-related AEs, and discontinuations due to AEs, comparable to that of vehicle
  - There were no treatment-related serious AEs
  - Roflumilast cream was well-tolerated with a low rate of application-site reactions
  - Local tolerability was highly favorable as reported by patient and investigator assessment of irritation, burning, and stinging

Table 3. Safety

	DERMIS-1		DERMIS-2	
n (%)	Roflumilast Cream 0.3% (n=286)	Vehicle (n=153)	Roflumilast Cream 0.3% (n=290)	Vehicle (n=152)
Patients with any TEAE	72 (25.2)	36 (23.5)	75 (25.9)	28 (18.4)
Patients with any treatment-related TEAE	7 (2.4)	3 (2.0)	16 (5.5)	8 (5.3)
Patients with any SAE	2 (0.7)	1 (0.7)	0	1 (0.7)
Patients who discontinued study due to AE	5 (1.7)	2 (1.3)	1 (0.3)	2 (1.3)
Most common TEAE (>2% in any group), preferred term				
Hypertension	5 (1.7)	6 (3.9)	4 (1.4)	0
Headache	3 (1.0)	2 (1.3)	11 (3.8)	1 (0.7)
Diarrhea	10 (3.5)	0	8 (2.8)	0
Psoriasis	0	3 (2.0)	1 (0.3)	0
Nasopharyngitis	5 (1.7)	3 (2.0)	1 (0.3)	1 (0.7)

Data are presented for safety population.
AE: adverse event; SAE: serious adverse event; TEAE: treatment-emergent adverse event.

CONCLUSIONS

- Once-daily roflumilast cream demonstrated robust and clinically meaningful efficacy based on IGA Success at the primary endpoint of 8 weeks
  - Results were reproducible across both phase 3 studies
- Roflumilast cream demonstrated statistically superior efficacy versus vehicle in patients with intertriginous area involvement, with most patients achieving I-IGA=0 (clear)
- Roflumilast cream significantly improved itch as early as 2 weeks (the earliest timepoint measured) using a clinically meaningful measure of a 4-point reduction in patients with WI-NRS ≥4 at baseline
- Roflumilast cream was well-tolerated with low rates of treatment-related AEs, serious AEs, and discontinuations due to AEs
  - Occurrence of application-site pain was low and comparable to vehicle
- These phase 3 studies demonstrated that investigational, once-daily roflumilast cream 0.3% has the potential to address many of the shortcomings of existing topical treatments for plaque psoriasis

REFERENCES

1. Elmets CA, et al. *J Am Acad Dermatol* 2021;84:432-470.
2. Lebwohl MG, et al. *N Engl J Med* 2020;383:229-239.

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DISCLOSURES

ML, **LHK**, **AM**, **LSG**, **ZDD**, **MJG**, **KAP**, **JB**, **NB**, **JDR**, **LKF**, **LJG**, **AAH**, **TJ**, **SEK**, **DMP**, **PSY**, and **MZ** are investigators and/or consultants for Arcutis Biotherapeutics, Inc. and received grants/research funding and/or honoraria; **PB**, **RCH**, **LN**, and **DRB** are or were employees of Arcutis Biotherapeutics, Inc. Additional disclosures provided on request.